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FILE 'CAPLUS' ENTERED AT 09:34:43 ON 20 MAY 2004
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FILE COVERS 1907 - 20 May 2004  VOL 140 ISS 21
FILE LAST UPDATED: 19 May 2004  (20040519/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

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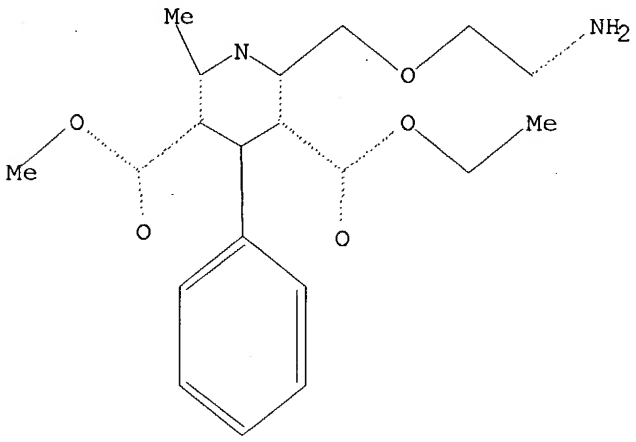


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L5            2 SEA FILE=CAPLUS L4 AND ETHANESULF?

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L5   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:        2004:101138  CAPLUS
DOCUMENT NUMBER:         140:151989
TITLE:                   Preparation amlodipine ethanesulfonate for
                         dosage forms
INVENTOR(S):             Cho, Seong-Hwan; Youn, Yong-Sik; Jung, Yun-Taek; Park,
                         Choong-Sil; Lee, Hyuk-Koo; Lee, Kwang-Hyeg; Jeong,
                         Eun-Ju; Kim, Young-Hoon; Jin, Hae-Tak; Cheon, Jun-Hee;
                         Lee, Sung-Hak; Jung, Sung-Hak; Lim, Dong-Kwon; Yeon,
```

Kyu-Jeong; Kim, Yun-Cheul; Park, Kyung-Mi; Kang, Hyun-Suk
PATENT ASSIGNEE(S): CJ Corp., S. Korea
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004011435	A1	20040205	WO 2003-KR1524	20030730

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004029931	A1	20040212	US 2003-628268	20030729

PRIORITY APPLN. INFO.: KR 2002-44858 A 20020730

AB Prepn. of amlodipine **ethanesulfonate** as a cryst. solid (yield 90%) and its physicochem. properties and pharmaceutical compns., such as capsules and tablets, for treatment of cardiac ischemia are described.

IT **652970-52-0P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn., properties and dosage forms of amlodipine **ethanesulfonate**)

RN 652970-52-0 CAPLUS
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, monoethanesulfonate (9CI) (CA INDEX NAME)

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CRN 88150-42-9
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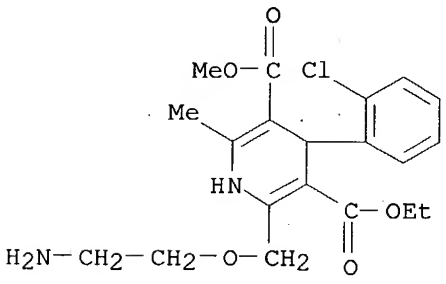

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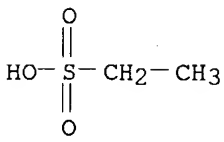
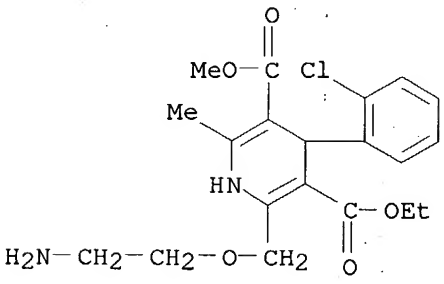


IT **88150-42-9**, Amlodipine
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn., properties and dosage forms of amlodipine **ethanesulfonate**)
RN 88150-42-9 CAPLUS
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:41231 CAPLUS
DOCUMENT NUMBER: 140:111429
TITLE: Preparation of substituted heterocyclic derivatives useful as antidiabetic and antiobesity agents
INVENTOR(S): Cheng, Peter T. W.; Chen, Sean; Devasthale, Pratik; Ding, Charles Z.; Herpin, Timothy F.; Wu, Shung; Zhang, Hao; Wang, Wei; Ye, Xiang-Yang
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 543 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004004665	A2	20040115	WO 2003-US22149	20030702
WO 2004004665	A3	20040325		

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KZ, MD, RU, TJ
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2004063700 A1 20040401 US 2003-616365 20030708
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OTHER SOURCE(S): MARPAT 140:111429
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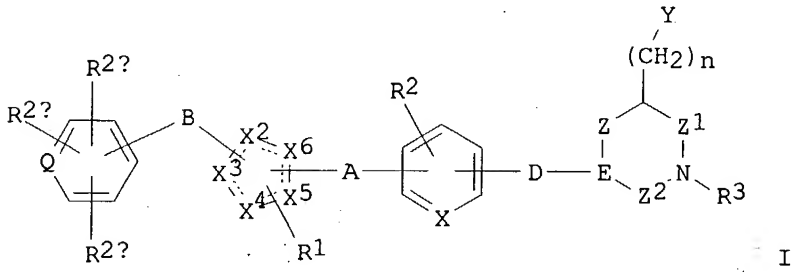

I

AB The title compds. (I) [Z1 = (CH2)q, CO; Z2 = (CH2)p, CO; D = CH, CO, (CH2)m (where m = 0-3; p = 1, 2; q = 0-2); n = 0-2; Q = C, N; A = (CH2)x (where x = 1-5); A = (CH2)x1 (where x1 = 1-5) with an alkenyl bond or an alkynyl bond embedded anywhere in the chain; or A = -(CH2)x2-O-(CH2)x3- (where X2, X3 = 0 to 5, provided that at least one of x2 and x3 is other than 0); B = a bond or (CH2)x4 (where x4 = 1-5); X = CH, N; X2-X6 = C, N, O, or S and at least one of X2-X6 is C; R1 = H, alkyl; R2 = H, alkyl, alkoxy, halogen, (un)substituted amino; R2a, R2b, R2c = H, alkyl, alkoxy, halogen, (un)substituted amino, cyano; R3 = H, alkyl, arylalkyl, aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, arylcarbonyl, alkylcarbonyl, aryl, heteroaryl, cycloheteroalkyl, etc.; E = CH, N; Z = (CH2)x5 (where x5 is 0, i.e. a single or a double bond, 1, 2), or Z is (CH2)x6 (where x6 = 2-5), where (CH2)x6 includes an alkenyl (C:C) bond embedded within the chain or Z = -(CH2)x7-O-(CH2)x8- (where x7, x8 = 0-4); (CH2)x to (CH2)x8, (CH2)m, (CH2)n, (CH2)p and (CH2)q may be optionally substituted; Y = CO2R4 (where R4 = H, alkyl, or a prodrug ester), or Y = a C-linked 1-tetrazole, a phosphinic acid of the structure P(O)(OR4a)R5 [where R4a = H, a prodrug ester; R5 = alkyl or aryl, or a phosphonic acid of the structure P(O)(OR4a)2]] including all stereoisomers, prodrug esters, and pharmaceutically acceptable salts thereof are prepd. These compds., e.g. cis-1-ethoxycarbonyl-4-[3-[2-(2-phenyl-5-methyloxazol-4-yl)ethoxy]phenyl]pyrrolidin-3-ylacetic acid and cis-1-(6-trifluoromethylpyrimidin-2-yl)-4-[3-[2-(2-phenyl-5-methyloxazol-4-yl)ethoxy]phenyl]pyrrolidine-3-carboxylic acid, modulate serum levels of blood glucose, triglyceride, insulin, and nonesterified fatty acid (NEFA) levels, and thus are particularly useful in the treatment of diabetes and obesity, esp. Type 2 diabetes, as well as hyperglycemia, hyperinsulinemia, hyperlipidemia, obesity, atherosclerosis, and related diseases employing such substituted acid derivs. alone or in combination with another antidiabetic agent and/or a hypolipidemic agent and/ or other therapeutic agents. Disclosed is a method for treating diabetes, esp. Type 2 diabetes, and related diseases such as insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, inflammation, Syndrome X, diabetic complications, dysmetabolic syndrome, atherosclerosis, and

related diseases, which comprises administering to a patient in need of treatment a therapeutically effective amt. of the compd. I. Also disclosed is a method for treating early malignant lesions (such as ductal carcinoma in situ of the breast and lobular carcinoma in situ of the breast), premalignant lesions including fibroadenoma of the breast and prostatic intraepithelial neoplasia (PIN), liposarcomas and various other epithelial tumors (including breast, prostate, colon, ovarian, gastric and lung), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and osteoporosis and proliferative diseases such as psoriasis, which comprises administering to a patient in need of treatment a therapeutically effective amt. of the compd. I.

IT **111470-99-6**, Amlodipine besylate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy; prepn. of substituted heterocyclic derivs. as antidiabetic and antiobesity agents)

RN 111470-99-6 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, monobenzenesulfonate (9CI) (CA INDEX NAME)

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CRN 88150-42-9
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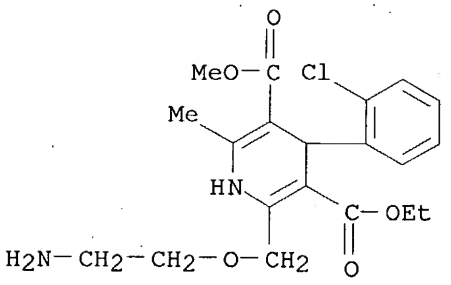

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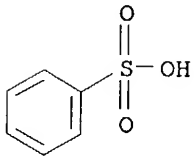

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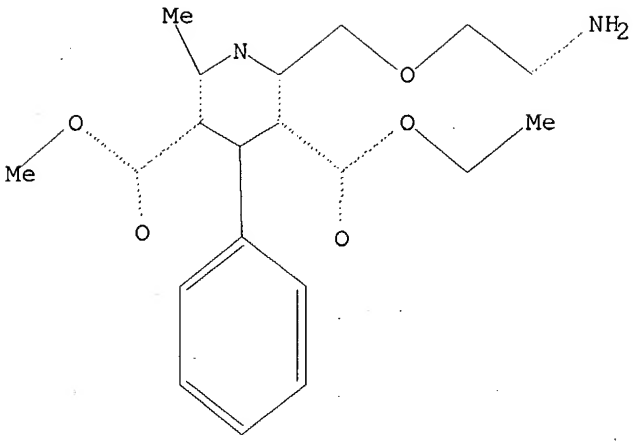

Structure attributes must be viewed using STN Express query preparation.
L3 176 SEA FILE=REGISTRY SSS FUL L1
L4 1402 SEA FILE=CAPLUS L3
L6 18 SEA FILE=CAPLUS L4 AND ETHANE?

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L6 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:101138 CAPLUS
DOCUMENT NUMBER: 140:151989
TITLE: Preparation amlodipine **ethanesulfonate** for dosage forms
INVENTOR(S): Cho, Seong-Hwan; Youn, Yong-Sik; Jung, Yun-Taek; Park, Choong-Sil; Lee, Hyuk-Koo; Lee, Kwang-Hyeg; Jeong, Eun-Ju; Kim, Young-Hoon; Jin, Hae-Tak; Cheon, Jun-Hee; Lee, Sung-Hak; Jung, Sung-Hak; Lim, Dong-Kwon; Yeon, Kyu-Jeong; Kim, Yun-Cheul; Park, Kyung-Mi; Kang, Hyun-Suk
PATENT ASSIGNEE(S): CJ Corp., S. Korea
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004011435	A1	20040205	WO 2003-KR1524	20030730

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004029931	A1	20040212	US 2003-628268	20030729

PRIORITY APPLN. INFO.: KR 2002-44858 A 20020730

AB Prepn. of amlodipine **ethanesulfonate** as a cryst. solid (yield 90%) and its physicochem. properties and pharmaceutical compns., such as capsules and tablets, for treatment of cardiac ischemia are described.

IT **652970-52-0P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn., properties and dosage forms of amlodipine **ethanesulfonate**)

RN 652970-52-0 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, monoethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 88150-42-9
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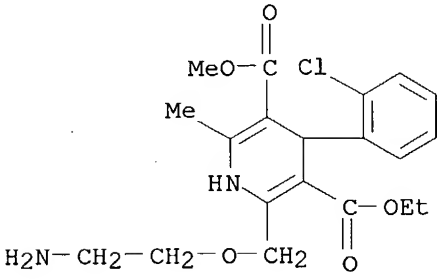

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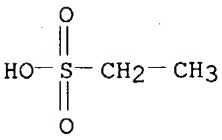
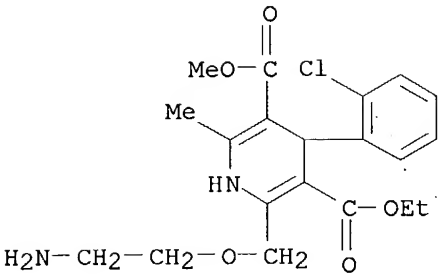


IT **88150-42-9**, Amlodipine
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn., properties and dosage forms of amlodipine **ethanesulfonate**)

RN 88150-42-9 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:41231 CAPLUS
DOCUMENT NUMBER: 140:111429
TITLE: Preparation of substituted heterocyclic derivatives useful as antidiabetic and antiobesity agents
INVENTOR(S): Cheng, Peter T. W.; Chen, Sean; Devasthale, Pratik; Ding, Charles Z.; Herpin, Timothy F.; Wu, Shung; Zhang, Hao; Wang, Wei; Ye, Xiang-Yang
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 543 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004004665	A2	20040115	WO 2003-US22149	20030702
WO 2004004665	A3	20040325		

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004063700	A1	20040401	US 2003-616365	20030708

PRIORITY APPLN. INFO.: US 2002-394508P P 20020709
OTHER SOURCE(S): MARPAT 140:111429
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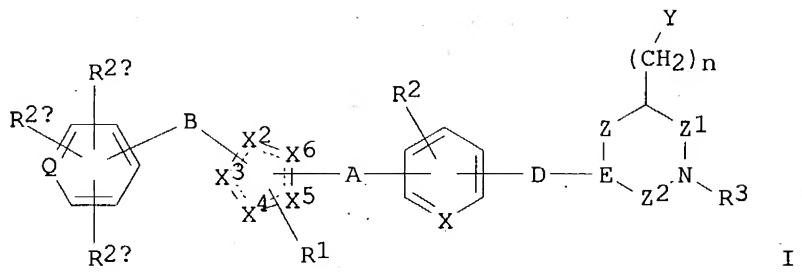


I

AB The title compds. (I) [Z1 = (CH2)q, CO; Z2 = (CH2)p, CO; D = CH, CO, (CH2)m (where m = 0-3; p = 1, 2; q = 0-2); n = 0-2; Q = C, N; A = (CH2)x (where x = 1-5); A = (CH2)x1 (where x1 = 1-5) with an alkenyl bond or an alkynyl bond embedded anywhere in the chain; or A = -(CH2)x2-O-(CH2)x3- (where X2, X3 = 0 to 5, provided that at least one of x2 and x3 is other than 0); B = a bond or (CH2)x4 (where x4 = 1-5); X = CH, N; X2-X6 = C, N, O, or S and at least one of X2-X6 is C; R1 = H, alkyl; R2 = H, alkyl, alkoxy, halogen, (un)substituted amino; R2a, R2b, R2c = H, alkyl, alkoxy, halogen, (un)substituted amino, cyano; R3 = H, alkyl, arylalkyl, aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, arylcarbonyl, alkylcarbonyl, aryl, heteroaryl, cycloheteroalkyl, etc.; E = CH, N; Z = (CH2)x5 (where x5 is 0, i.e. a single or a double bond, 1, 2), or Z is (CH2)x6 (where x6 = 2-5), where (CH2)x6 includes an alkenyl (C:C) bond embedded within the chain or Z = -(CH2)x7-O-(CH2)x8- (where x7, x8 = 0-4); (CH2)x to (CH2)x8, (CH2)m, (CH2)n, (CH2)p and (CH2)q may be optionally substituted; Y = CO2R4 (where R4 = H, alkyl, or a prodrug ester), or Y = a C-linked 1-tetrazole, a phosphinic acid of the structure P(O)(OR4a)R5 [where R4a = H, a prodrug ester; R5 = alkyl or aryl, or a phosphonic acid of the structure P(O)(OR4a)2]] including all stereoisomers, prodrug esters, and pharmaceutically acceptable salts thereof are prepd. These compds., e.g. cis-1-ethoxycarbonyl-4-[3-[2-(2-phenyl-5-methyloxazol-4-yl)ethoxy]phenyl]pyrrolidin-3-ylacetic acid and cis-1-(6-trifluoromethylpyrimidin-2-yl)-4-[3-[2-(2-phenyl-5-methyloxazol-4-yl)ethoxy]phenyl]pyrrolidine-3-carboxylic acid, modulate serum levels of blood glucose, triglyceride, insulin, and nonesterified fatty acid (NEFA) levels, and thus are particularly useful in the treatment of diabetes and obesity, esp. Type 2 diabetes, as well as hyperglycemia, hyperinsulinemia, hyperlipidemia, obesity, atherosclerosis, and related diseases employing such substituted acid derivs. alone or in combination with another antidiabetic agent and/or a hypolipidemic agent and/ or other therapeutic agents. Disclosed is a method for treating diabetes, esp. Type 2 diabetes, and related diseases such as insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, inflammation, Syndrome X, diabetic complications, dysmetabolic syndrome, atherosclerosis, and related diseases, which comprises administering to a patient in need of treatment a therapeutically effective amt. of the compd. I. Also disclosed is a method for treating early malignant lesions (such as ductal carcinoma in situ of the breast and lobular carcinoma in situ of the breast), premalignant lesions including fibroadenoma of the breast and prostatic intraepithelial neoplasia (PIN), liposarcomas and various other epithelial tumors (including breast, prostate, colon, ovarian, gastric and lung), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and osteoporosis and proliferative diseases such as psoriasis, which comprises administering to a patient in need of treatment a therapeutically effective amt. of the compd. I.

IT **111470-99-6**, Amlodipine besylate

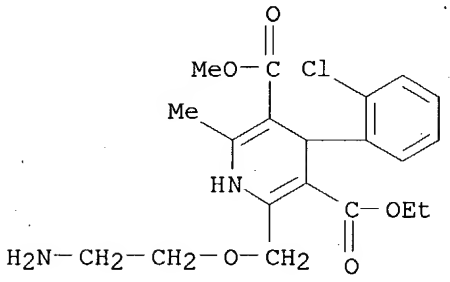
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy; prepn. of substituted heterocyclic derivs. as antidiabetic and antiobesity agents)

RN 111470-99-6 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, monobenzenesulfonate (9CI) (CA INDEX NAME)

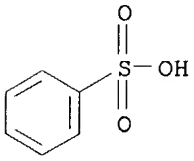
CM 1

CRN 88150-42-9
CMF C20 H25 Cl N2 O5



CM 2

CRN 98-11-3
CMF C6 H6 O3 S



L6 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:747138 CAPLUS
DOCUMENT NUMBER: 139:392238
TITLE: Toxicological Screening with Formula-Based Metabolite Identification by Liquid Chromatography/Time-of-Flight Mass Spectrometry
AUTHOR(S): Pelander, Anna; Ojanperae, Ilkka; Laks, Suvi; Rasanen, Ilpo; Vuori, Erkki
CORPORATE SOURCE: Department of Forensic Medicine, University of Helsinki, FIN-00014, Finland
SOURCE: Analytical Chemistry (2003), 75(21), 5710-5718
CODEN: ANCHAM; ISSN: 0003-2700
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

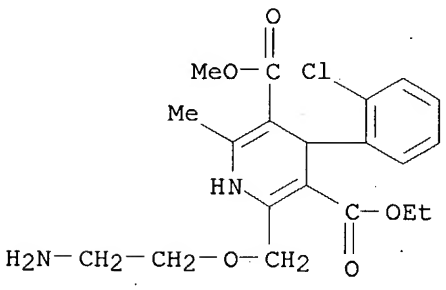
AB An anal. procedure was evaluated for the comprehensive toxicol. screening of drugs, metabolites, and pesticides in 1-mL urine samples by TurboIon spray liq. chromatog./time-of-flight mass spectrometry (LC/TOFMS) in the pos. ionization mode and continuous mass measurement. The substance

database consisted of exact monoisotopic masses for 637 compds., of which an LC retention time was available for 392. A macroprogram was refined for extg. the data into a legible report, utilizing metabolic patterns and preset identification criteria. These criteria included .+-.30 ppm mass tolerance, a .+-.0.2-min window for abs. retention time, if available, and a min. area count of 500. The limit of detection, detd. for 90 compds., was <0.1 mg/L for 73% of the compds. studied and >1.0 mg/L for 6% of the compds. For method comparisons, 50 successive autopsy urine samples were analyzed by this method, and the results confirmed by gas chromatog./mass spectrometry (GC/MS). Findings for parent drugs were consistent with both methods; in addn., LC/TOFMS regularly revealed apparently correct findings for metabolites not shown by GC/MS. Mean and median mass accuracy by LC/TOFMS was 7.6 and 5.4 ppm, resp. The procedure proved well-suited for tentative identification without ref. substances. The few false positives emphasized the fact that all three parameters, exact mass, retention time, and metabolite pattern, are required for unequivocal identification.

IT **88150-42-9**, Amlodipine
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(toxicol. screening of drugs and metabolites in urine samples with formula-based metabolite identification by liq. chromatog./time-of-flight mass spectrometry)

RN 88150-42-9 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:490947 CAPLUS
DOCUMENT NUMBER: 139:74009
TITLE: Controlled release pharmaceuticals containing polymer-bound drugs
INVENTOR(S): Corcoran, Robert C.
PATENT ASSIGNEE(S): The University of Wyoming, USA
SOURCE: PCT Int. Appl., 118 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003051113	A1	20030626	WO 2002-US40207	20021216

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-341153P P 20011214

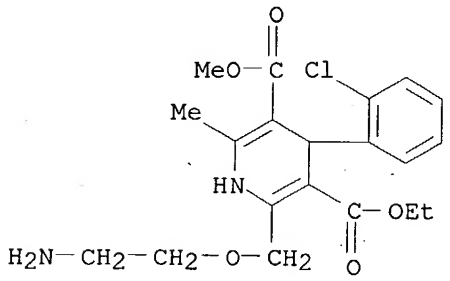
OTHER SOURCE(S): MARPAT 139:74009

AB This invention provides a method and compns. for the controlled release of drugs that have been attached by means of a covalent bond to a polymer or other moiety that blocks activity of the drug until it has been released. A 2-stage process is provided in which an unmasking reaction results in the formation of a chem. group that can then undergo a second reaction to release the drug. Thus, the narcotic analgesic fentanyl covalently attached to an inert polymer by way of its nitrogen through the formation of a quaternary vinylammonium salt, and then released by a sequence involving hydrolysis of an acetal that exposes an alc. that may then undergo an intramol. nucleophilic substitution reaction involving displacement of the nitrogen of oxycodone. The rate of this process may be controlled by controlling either or both of the rates of the acetal hydrolysis or the intramol. substitution reaction, but is preferably controlled by the latter through varying the no. of atoms in the chain connecting the alc. group and the vinylic carbon, as well as by the addn. of substituents on that chain. The drug-delivery mols. of this invention are useful for release of amine, alc. and thiol drugs, including a no. of narcotic analgesics, tricyclic amine antidepressants, and many others.

IT **88150-42-9D**, Amlodipine, polymer-bound
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(controlled release pharmaceuticals contg. polymer-bound drugs)

RN 88150-42-9 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:556104 CAPLUS

DOCUMENT NUMBER: 137:109489

TITLE: Compositions comprising a polypeptide and an active agent

INVENTOR(S): Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randal J.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 34 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002099013	A1	20020725	US 2001-933708	20010822
US 2004087483	A1	20040506	US 2002-136433	20020502

PRIORITY APPLN. INFO.:

US 2000-247556P	P	20001114
US 2000-247558P	P	20001114
US 2000-247559P	P	20001114
US 2000-247560P	P	20001114
US 2000-247561P	P	20001114
US 2000-247594P	P	20001114
US 2000-247595P	P	20001114
US 2000-247606P	P	20001114
US 2000-247607P	P	20001114
US 2000-247608P	P	20001114
US 2000-247609P	P	20001114
US 2000-247610P	P	20001114
US 2000-247611P	P	20001114
US 2000-247612P	P	20001114
US 2000-247620P	P	20001114
US 2000-247621P	P	20001114
US 2000-247634P	P	20001114
US 2000-247635P	P	20001114
US 2000-247698P	P	20001114
US 2000-247699P	P	20001114
US 2000-247700P	P	20001114
US 2000-247701P	P	20001114
US 2000-247702P	P	20001114
US 2000-247797P	P	20001114
US 2000-247798P	P	20001114
US 2000-247799P	P	20001114
US 2000-247800P	P	20001114
US 2000-247801P	P	20001114
US 2000-247802P	P	20001114
US 2000-247803P	P	20001114
US 2000-247804P	P	20001114
US 2000-247805P	P	20001114
US 2000-247807P	P	20001114
US 2000-247832P	P	20001114
US 2000-247833P	P	20001114
US 2000-247926P	P	20001114
US 2000-247927P	P	20001114
US 2000-247928P	P	20001114
US 2000-247929P	P	20001114
US 2000-247930P	P	20001114
US 2000-642820	A2	20000822
US 2000-248607P	P	20001116
US 2001-933708	A2	20010822

AB Claimed are compns. comprising a polypeptide and an active agent covalently attached to the polypeptide and a method for delivery of an active agent to a patient by administering the compn. to the patient. The peptide is a homopolymer of a naturally occurring amino acid or a heteropolymer of two or more naturally occurring amino acids. In an example, (Glu)n-cephalexin was prepd. from Glu(OBut)NCA and cephalexin hydrochloride.

IT **111470-99-6**, Amlodipine besylate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)
RN 111470-99-6 CAPLUS
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, monobenzenesulfonate (9CI) (CA INDEX NAME)

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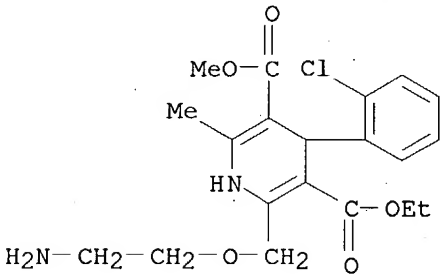
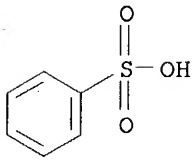
CRN 88150-42-9
CMF C20 H25 Cl N2 O5



CM 2

CRN 98-11-3
CMF C6 H6 O3 S



L6 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:555334 CAPLUS
DOCUMENT NUMBER: 137:114525
TITLE: Syntactic deformable pharmaceutical foam compositions
INVENTOR(S): Odidi, Isa; Odidi, Amina
PATENT ASSIGNEE(S): Can.
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002056861	A2	20020725	WO 2002-CA54	20020117
WO 2002056861	A3	20021017		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

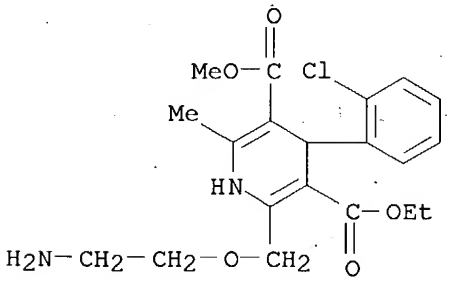
PRIORITY APPLN. INFO.: US 2001-765783 A 20010119

AB The invention relates to methods for prepg. a syntactic foam compn. suitable for use as a carrier for chems. or other compds., including pharmaceuticals. Carbopol 971P, hydroxyethyl cellulose, cellulose microspheres and silica, was mixed in a high-shear mixer. The resulting admixt. was treated with 2-propanol, while simultaneously subjecting the admixt. to high-shear forces in the high-shear mixer. This mixing created a uniform stable syntactic deformable and compressible dendritic solid foam which could be shaped before drying. Metoprolol succinate was added to the above admixt. and subjected to high-shear agitation for 2 min before treatment with 2-propanol. A stable syntactic deformable and compressible dendritic solid foam which could be shaped before drying was obtained. This was dried at 40.degree.. The dried foam was the disentangled by size redn. to obtain discrete particles. The free flowing particles were reassembled and shaped by compression in a mold. The shaped units, when subjected to an aq. medium, released metoprolol over a period of .ltoreq.3 h.

IT **88150-42-9**, Amlodipine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(syntactic deformable pharmaceutical foam compns.).

RN 88150-42-9 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



L6 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:332011 CAPLUS

DOCUMENT NUMBER: 136:355482

TITLE: Compositions comprising a polypeptide and an active agent

INVENTOR(S): Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randall J.

PATENT ASSIGNEE(S): New River Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 11

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002034237	A1	20020502	WO 2001-US26142	20010822
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 6716452	B1	20040406	US 2000-642820	20000822
AU 2001086599	A5	20020506	AU 2001-86599	20010822
EP 1311242	A1	20030521	EP 2001-966056	20010822
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-642820 A 20000822
WO 2001-US26142 W 20010822

AB Claimed are compns. comprising a polypeptide and an active agent covalently attached to the polypeptide and a method for delivery of an active agent to a patient by administering the compn. to the patient. The peptide is a homopolymer of a naturally occurring amino acid or a heteropolymer of two or more naturally occurring amino acids. In an example, (Glu)n-cephalexin was prepd. from Glu(OBut)NCA and cephalexin hydrochloride.

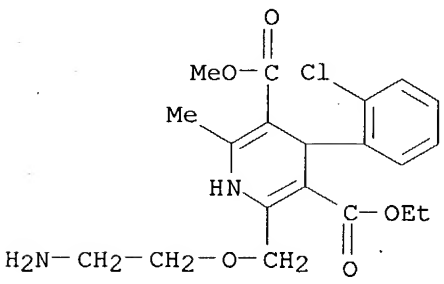
IT **111470-99-6**, Amlodipine besylate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

RN 111470-99-6 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, monobenzenesulfonate (9CI) (CA INDEX NAME)

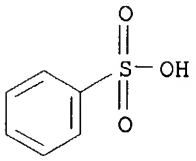
CM 1

CRN 88150-42-9
CMF C20 H25 Cl N2 O5



CM 2

CRN 98-11-3
CMF C6 H6 O3 S



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:725436 CAPLUS
DOCUMENT NUMBER: 133:301171
TITLE: Compositions and methods for improved delivery of ionizable hydrophobic therapeutic agents
INVENTOR(S): Chen, Feng-jing; Patel, Manesh V.
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

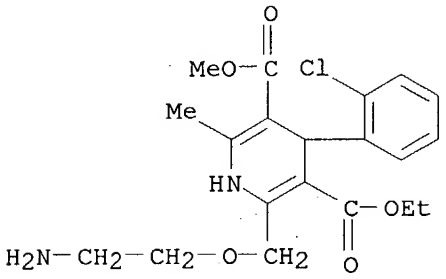
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059475	A1	20001012	WO 2000-US7342	20000316
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6383471	B1	20020507	US 1999-287043	19990406
EP 1165048	A1	20020102	EP 2000-916547	20000316
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1999-287043 A 19990406
WO 2000-US7342 W 20000316

AB The present invention is directed to a pharmaceutical compn. including a hydrophobic therapeutic agent having at least one ionizable functional group, and a carrier. The carrier includes an ionizing agent capable of ionizing the functional group, a surfactant, and optionally solubilizers, triglycerides, and neutralizing agents. The invention further relates to a method of prepg. such compns. by providing a compn. of an ionizable hydrophobic therapeutic agent, an ionizing agent, and a surfactant, and neutralizing a portion of the ionizing agent with a neutralizing agent. The compns. of the invention are particularly suitable for use in oral dosage forms. A carrier contg. concd. phosphoric acid 0.025, Tween-20 0.3, Arlacel 186 0.2, sodium taurocholate 0.15, propylene glycol 0.3 g was formulated. Itraconazole was included in the carrier at 30 mg/mL for testing the stability of the itraconazole soln. upon diln. in simulated gastric fluid.

IT **88150-42-9**, Amlodipine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. contg. hydrophobic therapeutic agents and

carriers contg. ionizing agents and surfactants and triglycerides)
RN 88150-42-9 CAPLUS
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:608551 CAPLUS
DOCUMENT NUMBER: 133:213151
TITLE: Pharmaceutical compositions and methods for improved delivery of hydrophobic therapeutic agents
INVENTOR(S): Patel, Manesh V.; Chen, Feng-Jing
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050007	A1	20000831	WO 2000-US165	20000105
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6294192	B1	20010925	US 1999-258654	19990226
AU 2000022242	A5	20000914	AU 2000-22242	20000105
AU 771659	B2	20040401		
NZ 513810	A	20010928	NZ 2000-513810	20000105
EP 1158959	A1	20011205	EP 2000-901394	20000105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537317	T2	20021105	JP 2000-600619	20000105

PRIORITY APPLN. INFO.: US 1999-258654 A 19990226
WO 2000-US165 W 20000105

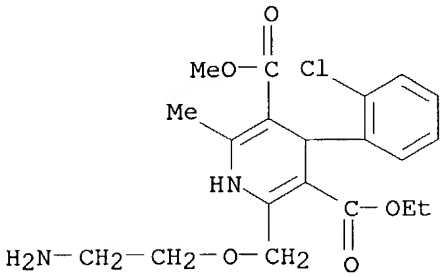
AB The present invention relates to triglyceride-free pharmaceutical compns. for delivery of hydrophobic therapeutic agents. Compns. of the present invention include a hydrophobic therapeutic agent and a carrier, where the

carrier is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon diln. with an aq. solvent, the compn. forms a clear, aq. dispersion of the surfactants contg. the therapeutic agent. The invention also provides methods of treatment with hydrophobic therapeutic agents using these compns. A pharmaceutical compn. contained cyclosporin 0.14, Cremophor RH-40 0.41, Arlacel186 0.29, sodium taurocholate 0.26, and propylene glycol 0.46 mg.

IT **88150-42-9**, Amlodipine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. and methods for improved delivery of hydrophobic therapeutic agents)

RN 88150-42-9 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:718374 CAPLUS
DOCUMENT NUMBER: 132:189478
TITLE: Effects of amlodipine on tubulointerstitial lesions in normotensive hyperoxaluric rats
AUTHOR(S): Toblli, Jorge Eduardo; Ferder, Leon; Angerosa, Margarita; Inserra, Felipe
CORPORATE SOURCE: Laboratory of Experimental Medicine, Hospital Aleman, Buenos Aires, 1122, Argent.
SOURCE: Hypertension (1999), 34(4, Pt. 2), 854-858
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

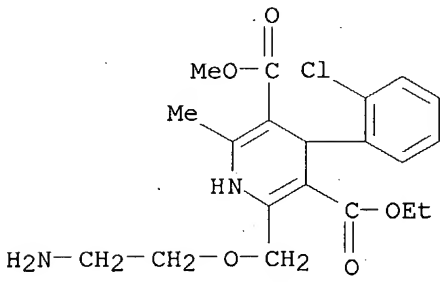
AB This study evaluated a possible beneficial effect of amlodipine, a 1,4-dihydropyridine-type calcium antagonist, in a model of primary tubulointerstitial lesion produced by hyperoxaluria. Two-month-old male Sprague-Dawley rats were sepd. into 4 groups for a 4-wk period: G1 (control; tap water only); G2 (hyperoxaluric); G3 (hyperoxaluric plus amlodipine treatment); and G4 (amlodipine treatment). G2 and G3 rats were given 1% ethylene glycol (a precursor for oxalates) in drinking water, and G3 and G4 rats were given amlodipine at 2 mg/kg/day by gavage. At the end of the study, semiquant. scores were used to evaluate the different renal tubulointerstitial lesions, urinary albumin excretion, renal function by creatinine clearance, and blood pressure. Rats belonging to the hyperoxaluric group treated with amlodipine (G3) had fewer tubulointerstitial lesions than the hyperoxaluric group untreated with amlodipine (G2). On the other hand, there were no significant changes in blood pressure in any group. These data suggest that amlodipine, probably

by nonhemodynamic mechanisms of action, can provide considerable benefit in the prevention of epithelial tubular cell injury and inflammatory response and therefore in the prevention of the progressive tubulointerstitial fibrosis caused by oxalates.

IT **88150-42-9**, Amlodipine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amlodipine effects on tubulointerstitial lesions in normotensive hyperoxaluric rats)

RN 88150-42-9 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:683500 CAPLUS

DOCUMENT NUMBER: 132:6301

TITLE: Synthesis, calcium channel antagonist activity, and anticonvulsant activity of 3-ethyl 5-methyl 1,4-dihydro-2-[(2-hydroxyethoxy)methyl]-6-methyl-4-(2,3-dichlorophenyl)-3,5-pyridinedicarboxylate coupled to a 1-methyl-1,4-dihydropyridyl-3-carbonyl chemical delivery system

AUTHOR(S): Yiu, Sai-Hay; Knaus, Edward E.

CORPORATE SOURCE: Faculty Pharmacy Pharmaceutical Sciences, Univ. Alberta, Edmonton, AB, T6G 2N8, Can.

SOURCE: Archiv der Pharmazie (Weinheim, Germany) (1999), 332(10), 363-367
CODEN: ARPMAS; ISSN: 0365-6233

PUBLISHER: Wiley-VCH Verlag GmbH

DOCUMENT TYPE: Journal

LANGUAGE: English

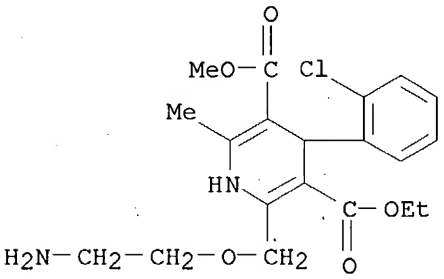
AB 3-Et 5-Me 1,4-dihydro-2-[(2-hydroxyethoxy)methyl]-6-methyl-4-(2,3-dichlorophenyl)-3,5-pyridinedicarboxylate (I), a bioisostere of amlodipine, was prepd. by the reaction of HO(CH2)2OCH2COCH2CO2Et with 2,3-Cl2C6H3CH:CAcCO2Me and NH4OAc. Compd. I was elaborated to the target product 3-Et 5-Me 1,4-dihydro-2-[2-[(1-methyl-1,4-dihydropyridyl-3-carbonyloxy)ethoxy]methyl]-6-methyl-4-(2,3-dichlorophenyl)-3,5-pyridinedicarboxylate (II). Compd. I (IC50 = 6.56.cntdot.10-9 M) was .apprx.44-fold more active as a Ca antagonist than the ref. drug nimodipine, but 4-fold less potent than felodipine. Compd. II is a slightly less potent Ca channel antagonist (IC50 = 2.99.cntdot.10-8 M) than parent I. Compds. I, II, felodipine, and nimodipine are highly lipophilic (Kp = 227, 344, 442, and 187, resp.). Compd. I exhibited

equipotent anticonvulsant activity to nimodipine in the maximal electroshock (MES) anticonvulsant screen. Unlike nimodipine, I provided modest protection in the s.c. metrazol (scMet) anticonvulsant screen. In contrast, II was inactive in both the MES and scMet screens.

IT **88150-42-9P**, Amlodipine
RL: BSU (Biological study, unclassified); PNU (Preparation, unclassified); BIOL (Biological study); PREP (Preparation)
(prepn. of bioisostere as calcium antagonist and anticonvulsant)

RN 88150-42-9 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:945865 CAPLUS

DOCUMENT NUMBER: 124:66370

TITLE: Contact angles and surface free energy parameters of some 1,4-dihydropyridine calcium antagonist powders

AUTHOR(S): Kerc, Janez; Srcic, Stane; Planinsek, Odon; Kofler, Bojan

CORPORATE SOURCE: Res. and Dev. Div., Lek D.D. Pharmaceutical and Chemical Co., Ljubljana, Slovenia

SOURCE: Farmacevtski Vestnik (Ljubljana) (1994), 45(4), 347-57
CODEN: FMVTAV; ISSN: 0014-8229

PUBLISHER: Slovensko Farmacevtsko Drustvo

DOCUMENT TYPE: Journal

LANGUAGE: English

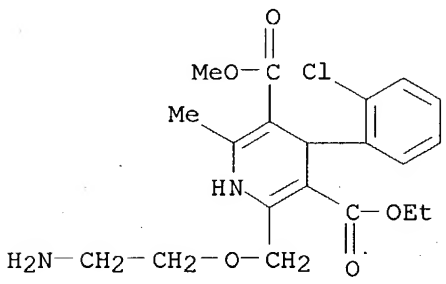
AB The contact angle was used as a measure of the wettability of a solid, and detns. were made on pharmaceutical powders by direct measurement of the angle formed by a drop of a liq. on the compacted powder of a drug substance. The investigated drug substances are analogs of the 1,4-dihydropyridine calcium antagonist group: nifedipine, nimodipine, felodipine, nicardipine HCl, and amlodipine benzenesulfonate. Various liqs. including water, ethylene glycol, and 30% ethanol, were used to measure powder polar forces and powder dispersion forces whose sum is the powder free surface energy which may serve to predict the soly. and dissoln. rater of the powder. The values of surface free energy of nifedipine, nimodipine and felodipine were found to be much lower comparing to those of nicardipine HCl and amlodipine benzenesulfonate. Moreover, powders with low free surface energy were found to have much lower soly. and dissoln. rate.

IT **111470-99-6**, Amlodipine benzenesulfonate
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(contact angles and surface free energy parameters of dihydropyridine

calcium antagonist powders)
RN 111470-99-6 CAPLUS
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, monobenzenesulfonate (9CI) (CA INDEX NAME)

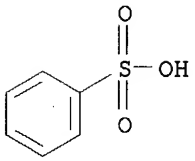
CM 1

CRN 88150-42-9
CMF C20 H25 Cl N2 O5



CM 2

CRN 98-11-3
CMF C6 H6 O3 S



L6 ANSWER 13 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:770566 CAPLUS
DOCUMENT NUMBER: 123:179219
TITLE: Contact angles and surface free energy parameters of some 1,4-dihydropyridine calcium antagonist powders
AUTHOR(S): Kerc, Janez; Srcic, Stane; Planinsek, Odon; Kofler, Bojan
CORPORATE SOURCE: Research and Development Division, Lek d.d., Pharmaceutical and Chemical Company, Ljubljana, Slovenia
SOURCE: Farmacevtski Vestnik (Ljubljana, Slovenia) (1994), 45(4), 347-57
CODEN: FMVTAV; ISSN: 0014-8229
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The contact angle was used as a measure of the wettability of a solid, and detns. were made on pharmaceutical powders by direct measurement of the angle formed by a drop of a liq. on the compacted powder of a drug substance. The investigated drug substances are analogs of the 1,4-dihydropyridine calcium antagonist group: nifedipine, nimodipine, felodipine, nicardipine HCl, and amlodipine benzenesulfonate. Various

liqs. including water, ethylene glycol, and 30% ethanol, were used to measure powder polar forces and powder dispersion forces whose sum is the powder free surface energy which may serve to predict the soly. and dissoln. rate of the powder. The values of surface free energy of nifedipine, nimodipine and felodipine were found to be much lower comparing to those of nicardipine HCl and amlodipine benzenesulfonate. Moreover, powders with low free surface energy were found to have much lower soly. and dissoln. rate.

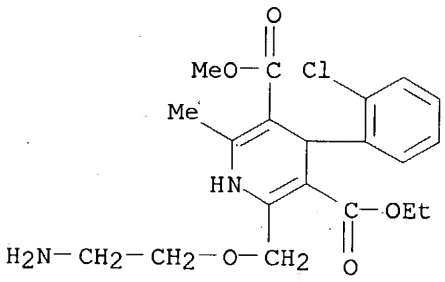
IT **111470-99-6**, Amlodipine benzenesulfonate
RL: PRP (Properties)
(wettability of dihydropyridine calcium antagonist powders)

RN 111470-99-6 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, monobenzenesulfonate (9CI) (CA INDEX NAME)

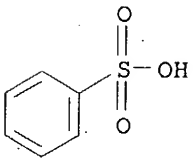
CM 1

CRN 88150-42-9
CMF C20 H25 Cl N2 O5



CM 2

CRN 98-11-3
CMF C6 H6 O3 S



L6 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:729623 CAPLUS
DOCUMENT NUMBER: 123:190633
TITLE: Capillary zone electrophoresis in a comprehensive screen for basic drugs in whole blood
AUTHOR(S): Hudson, J.C.; Golin, M.; Malcolm, M.
CORPORATE SOURCE: Toxicology Section, RCMP Forensic Laboratory, Regina, SK, S4P 3J7, Can.
SOURCE: Journal - Canadian Society of Forensic Science (1995), 28(2), 137-52
CODEN: JCFSBP; ISSN: 0008-5030

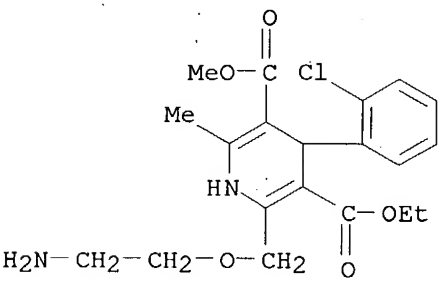
PUBLISHER: Canadian Society of Forensic Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Capillary zone electrophoresis (CZE) is shown to be capable of detecting a large no. of basic drugs at concns. considered to be forensically significant. A procedure for prepg. exts. of whole blood for anal. by CZE is presented. Relative migration times are presented for over 400 drugs, analyzed using 100 mmol/L phosphate run buffer of pH 2.5 and pH 9.5.

IT **88150-42-9**, Amlodipine
RL: ANT (Analyte); ANST (Analytical study)
(capillary zone electrophoresis in a comprehensive screen for basic drugs in whole blood)

RN 88150-42-9 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



L6 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:491470 CAPLUS
DOCUMENT NUMBER: 121:91470
TITLE: Cyclodextrin complexes of dihydropyridine calcium channel blockers
AUTHOR(S): Zmitek, J.; Fercej-Temeljotov, D.; Husu, B.; Kocjan, D.; Milivojevic, D.; Verhnjak, K.; Bukovec, P.
CORPORATE SOURCE: Res. and Dev. Dep., LEK d.d. Ljubljana, Pharm. and Chem. Co., Ljubljana, 61000, Slovenia
SOURCE: Minutes Int. Symp. Cyclodextrins, 6th (1992), 406-9. Editor(s): Hedges, Allan R. Ed. Sante: Paris, Fr. CODEN: 60BCAL
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Inclusion complexes of some racemic and enantiomerically pure dihydropyridine calcium channel blockers were prepd. with .beta.-cyclodextrin and some of its water sol. derivs. Besides usual methods also FAB mass spectrometry was used for complex characterization. NMR spectra allowed the authors to det. sites of complexation and to distinguish among racemic and enantiomeric complexes. Complexes of nicardipine hydrochloride (1:2) were also prepd. Water solubilities were improved considerably by complexation.

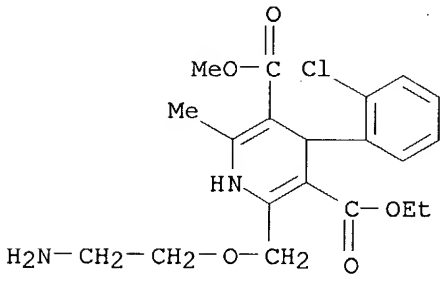
IT **111470-99-6D**, complexes with .beta.-cyclodextrins **156570-65-9**
RL: BIOL (Biological study)
(formation and soly. of)

RN 111470-99-6 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, monobenzenesulfonate (9CI) (CA INDEX NAME)

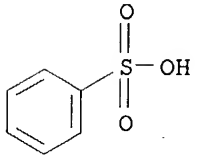
CM 1

CRN 88150-42-9
CMF C20 H25 Cl N2 O5



CM 2

CRN 98-11-3
CMF C6 H6 O3 S



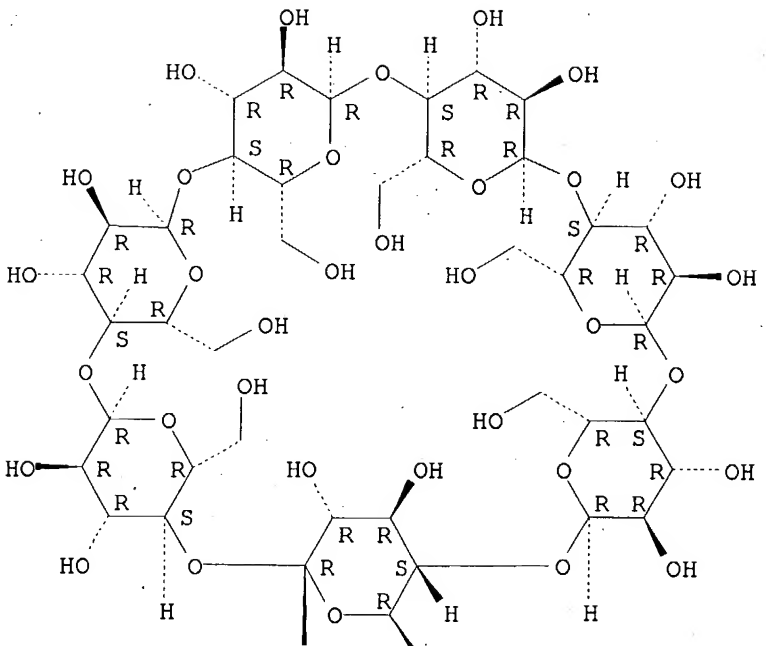
RN 156570-65-9 CAPLUS
CN .beta.-Cyclodextrin, compd. with 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate monobenzenesulfonate (1:1) (9CI) (CA INDEX NAME)

CM 1

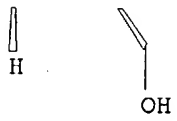
CRN 7585-39-9
CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

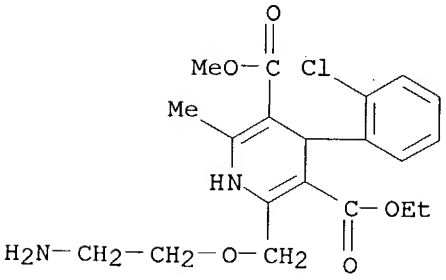


CM 2

CRN 111470-99-6
CMF C20 H25 Cl N2 O5 . C6 H6 O3 S

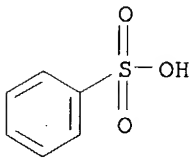
CM 3

CRN 88150-42-9
CMF C20 H25 Cl N2 O5

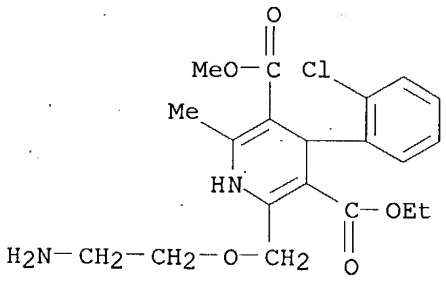


CM 4

CRN 98-11-3
CMF C6 H6 O3 S



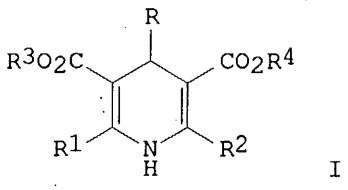
IT **88150-42-9**, Amlodipine
RL: PROC (Process)
(solubilization of, by complexation with .beta.-cyclodextrins)
RN 88150-42-9 CAPLUS
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



L6 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:38145 CAPLUS
DOCUMENT NUMBER: 120:38145
TITLE: Inclusion complexes of optically active and racemic 1,4-dihydropyridines with cyclodextrin derivatives
INVENTOR(S): Fercej-Temeljotov, Darja; Zmitek, Janko; Husu-Kovacevic, Breda; Kotnik, Sonja; Jerala-Strukelj, Zdenka
PATENT ASSIGNEE(S): Lek, Tovarna Farmacevtskih in Kemicnih Izdelkov, d.d., Slovenia
SOURCE: Eur. Pat. Appl., 60 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 566142	A1	19931020	EP 1993-106236	19930416
R: CH, DE, ES, FR, GB, IT, LI, NL				
AT 399718	B	19950725	AT 1992-795	19920416
JP 06100537	A2	19940412	JP 1993-90036	19930416
US 5519012	A	19960521	US 1994-357790	19941216

PRIORITY APPLN. INFO.: AT 1992-795 A 19920416
US 1993-44509 B1 19930409
OTHER SOURCE(S): MARPAT 120:38145
GI



I

AB Optically active and racemic 1,4-dihydropyridines (I; R = substituted Ph; R1, R2 = Me, 2-aminoethoxymethyl, cyano; R3. R4 = H, C1-6-alkyl, 2-methoxyethyl, styryl, furyl, etc) and their acid addn. salts are converted to inclusion compds. with Me .beta.-cyclodextrin, hydroxyethyl .beta.-cyclodextrin, hydroxypropyl .beta.-cyclodextrin, or .beta.-cyclodextrin to improve their water soly. The inclusion complexes are effective Ca antagonists for the treatment of hypertension, angina pectoris, and cerebrovascular disorders. Thus, (+)-nicardipine.cntdot.HCl-.beta.-cyclodextrin inclusion compd. (II) was prepd. Water soly. of II was 15.8 mg/mL as compared to 0.4 mg/mL for (+)-nicardipine.cntdot.HCl. A capsule contg. 38.1% II was formulated.

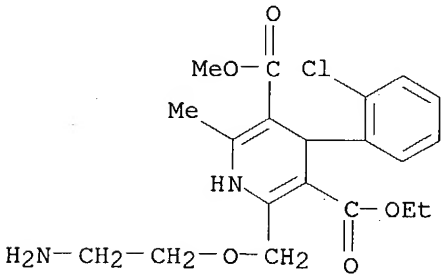
IT **88150-47-4DP**, Amlodipine maleate, inclusion complexes with Me .beta.-cyclodextrin **111470-99-6DP**, Amlodipine besylate, inclusion complexes with Me .beta.-cyclodextrin **152076-95-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and water soly. of)

RN 88150-47-4 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

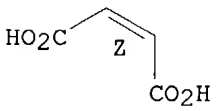
CRN 88150-42-9
CMF C20 H25 Cl N2 O5



CM 2

CRN 110-16-7
CMF C4 H4 O4

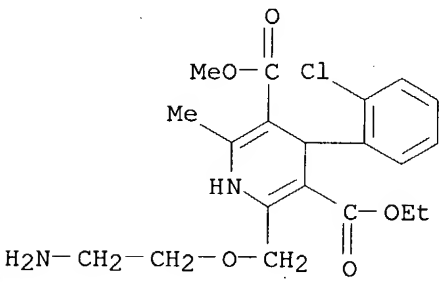
Double bond geometry as shown.



RN 111470-99-6 CAPLUS
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, monobenzenesulfonate (9CI) (CA INDEX NAME)

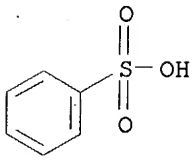
CM 1

CRN 88150-42-9
CMF C20 H25 Cl N2 O5



CM 2

CRN 98-11-3
CMF C6 H6 O3 S



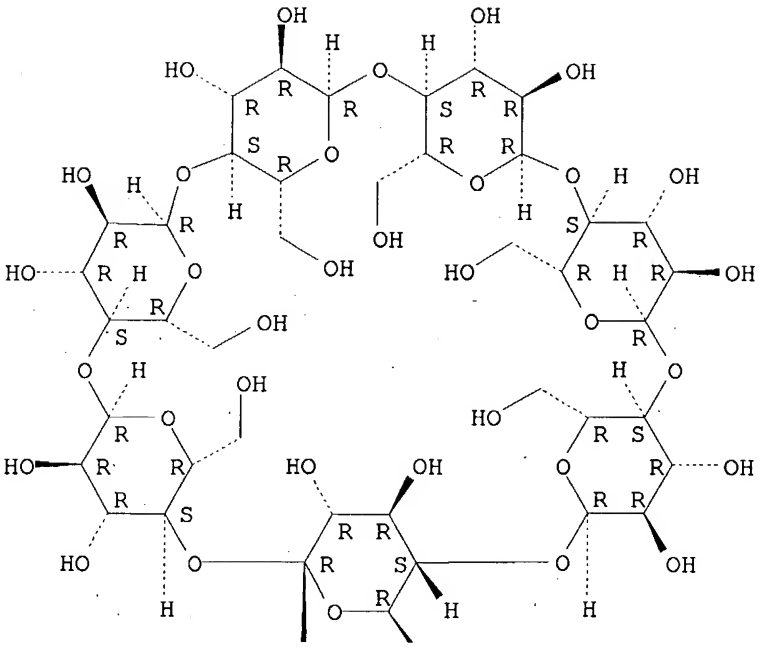
RN 152076-95-4 CAPLUS
CN .beta.-Cyclodextrin, compd. with 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate monobenzenesulfonate (9CI) (CA INDEX NAME)

CM 1

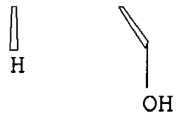
CRN 7585-39-9
CMF C42 H70 O35

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

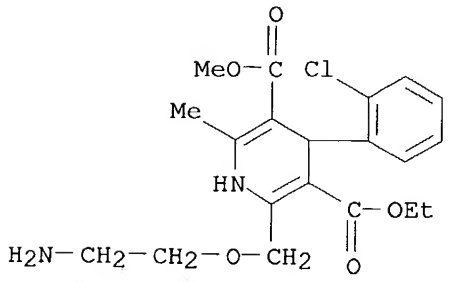


CM 2

CRN 111470-99-6
CMF C20 H25 Cl N2 O5 . C6 H6 O3 S

CM 3

CRN 88150-42-9
CMF C20 H25 Cl N2 O5



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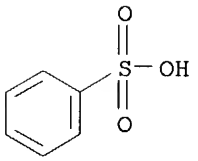
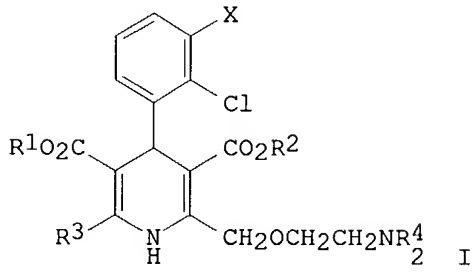
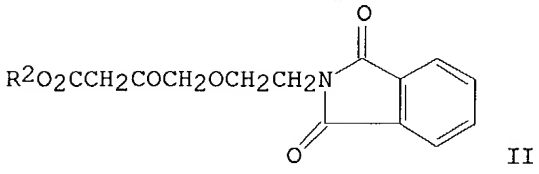


L6 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:173973 CAPLUS
DOCUMENT NUMBER: 116:173973
TITLE: Long-acting dihydropyridine calcium antagonists. 9. Structure activity relationships around amlodipine
AUTHOR(S): Alker, D.; Arrowsmith, J. E.; Campbell, S. F.; Cross, P. E.
CORPORATE SOURCE: Pfizer Cent. Res., Sandwich/Kent, CT13 9NJ, UK
SOURCE: European Journal of Medicinal Chemistry (1991), 26(9), 907-13
CODEN: EJMCA5; ISSN: 0223-5234
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



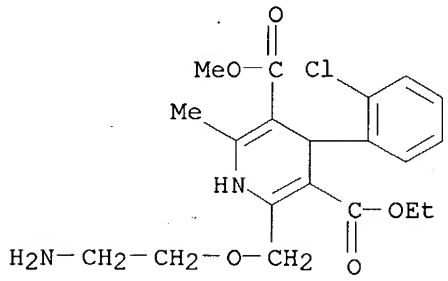
II

AB Phenylpyridinedicarboxylates I (R1 = Me, Et, MeOCH2CH2, etc., R2 = Et, Me, CMe3, CH2CF2CF3, etc., R3 = Me, CH2OMe, CH2SMe, CF3, cyano, CH2OCMe3, R4 = H, X = H, Cl) were prepd. and their calcium channel blocking activity and structure activity relationships were examd. Thus, condensation of R3C(NH2):CHCO2R1 with [(phthalimido)ethoxy]acetoacetates II and 2-ClC6H4CHO or 2,3-Cl2C6H3CHO gave I (NR42 = phthalimido) which were deprotected to give the free amine. Increasing the size of the C5 ester

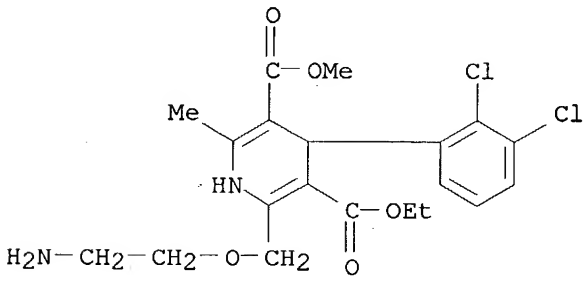
group dramatically reduces calcium antagonist activity.

IT **88150-42-9 88150-50-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(calcium channel blocking activity of)

RN 88150-42-9 CAPLUS
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)

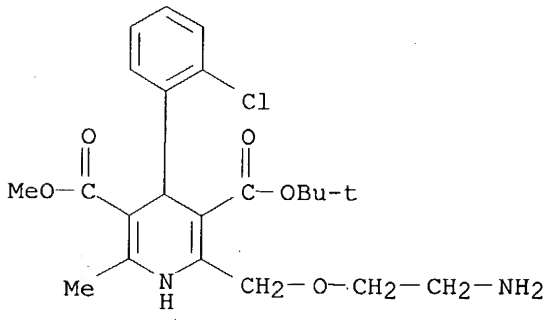


RN 88150-50-9 CAPLUS
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2,3-dichlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)

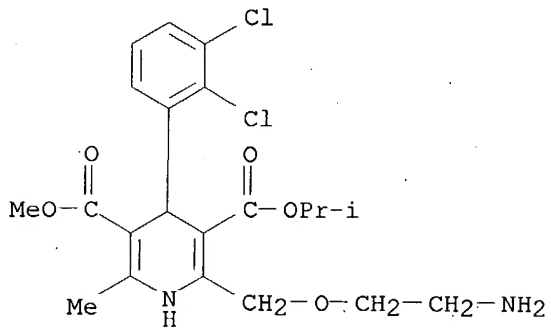


IT **140171-67-1P 140171-73-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and calcium channel-blocking activity of)

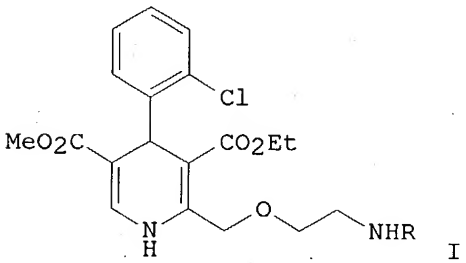
RN 140171-67-1 CAPLUS
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-(1,1-dimethylethyl) 5-methyl ester (9CI) (CA INDEX NAME)



RN 140171-73-9 CAPLUS
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2,3-dichlorophenyl)-1,4-dihydro-6-methyl-, 5-methyl 3-(1-methylethyl) ester (9CI) (CA INDEX NAME)



L6 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:55549 CAPLUS
DOCUMENT NUMBER: 112:55549
TITLE: Long-acting dihydropyridine calcium antagonists. 4. Synthesis and structure-activity relationships for a series of basic and nonbasic derivatives of 2[(2-aminoethoxy)methyl]-1,4-dihydropyridine calcium antagonists
AUTHOR(S): Alker, David; Campbell, Simon F.; Cross, Peter E.; Burges, Roger A.; Carter, Anthony J.; Gardiner, Donald G.
CORPORATE SOURCE: Pfizer Cent. Res., Sandwich/Kent, CT13 9NJ, UK
SOURCE: Journal of Medicinal Chemistry (1990), 33(2), 585-91
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 112:55549
GI



I

AB The prepn. of a series of 1,4-dihydropyridines (DHPs) which have polar, acyclic, nonbasic, and glycinamide substituents on an ethoxymethyl chain at the 2-position, e.g., I (R = 2-pyridylcarbonyl, CH2CONH2, CONHMe, Ac, SO2NH2, CONHCH2CONH2), from I (R = H) is described. The calcium antagonist activity on rat aorta of both these classes of DHP is compared with their neg. inotropic activity as detd. by using a Langendorff perfused guinea pig heart model. A no. of the compds. evaluated have

activity of the same order as nifedipine although those with more extended substituents have lower potency, particularly when a basic substituent is present. The compds. examd. displayed a wide variation in selectivity for vascular over cardiac tissue. A no. of structure-activity relationship trends were identified and possible explanations to account for the differences in selectivity obsd. are advanced. I (R = CH2CONH2) was identified as a potent (IC50 = 4 .times. 10-9M) calcium antagonist which is 20-fold selective for vascular over cardiac tissue and which has a markedly longer duration of action (>5 h) than nifedipine in the anesthetized dog on i.v. administration. The pharmacokinetic half-life of I (R = CH2CONH2) was established as 4.7 h and possible explanations are advanced to account for I (R = CH2CONH2) having a shorter plasma half-life than amlodipine and a longer plasma half-life than felodipine.

IT **88150-42-9**

RL: RCT (Reactant); RACT (Reactant or reagent)
(reactions of)

RN 88150-42-9 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)